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## CANCER OF THE LUNG FROM 1900 TO 1930

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INTEREST IN CANCER of the lung began in France with the publication, in 1810, of Bayle's article (10) and rapidly spread to England and Germany. Scientific interest continued to progress, as indicated by the number of publications, and by the beginning of the twentieth century it had already spread to many European countries and to the Americas. Between 1900 and 1930 many theses and dissertations on this subject were submitted to various faculties of medicine to fulfill academic requirements for advanced degrees. Reviews and monographs were beginning to appear and in 1928 an international symposium was held in London for a discussion of many problems referable to cancer of the lung. These discussions included the frequency, etiology, histogenesis, pathology, clinical diagnosis, and treatment. It would be of interest for all of us today to read the number of excellent contributions made by many investigators throughout the world between 1900 and 1930, and to know that men were just as interested at that time to establish the etiology, and to account for the increase in frequency, of cancer of the lung as we in the United States have been during the last few years.

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There can be only one thing accomplished by a review of the literature on cancer of the lung at this particular time and that is to collect and briefly emphasize some of the data published between 1900 and 1930. It seems to us that the inscription engraved in stone on each side of the north entrance of the Archives Building in Washington, D.C. is apropos to this problem of cancer of the lung: "What is past is prologue. Study the past."

Pepper (116), writing in 1850, said, "It is not until quite recently that this subject (of pulmonary cancer) has fully engaged the attention of the profession; hitherto, such cases were viewed as mere matters of medical curiosity 'not known to be in any degree influenced by medicine, and too rare to be of much practical importance.' There is good reason to believe, however, this disease is of much more frequent occurrence than is commonly supposed, and that in a vast majority of cases it entirely escapes detection, owing to the great difficulty which attends its diagnosis." Reinhard (126) found 27 published cases in 1878. Werner (168), in 1891, found 9 cases fully verified. Wolf (171), in 1895, reported 31 cases which had been diagnosed since 1885, and Pässler (115), in 1896, found 70 and added 4 of his own. Boecker (16), in 1910, estimated that about 100 cases could be found in the literature. Adler (2), in 1912, collected 374

cases of pulmonary carcinoma and 94 cases of pulmonary sarcoma. Weller (164), in 1913, collected 89 cases that he considered authentic primary carcinomas of the larger bronchi and investigated the pathological and clinical features of the group. In 1918, McMahon and Carman (102) found in the literature 428 cases which they considered to be authentic.

Difficulties and errors in the clinical diagnosis of lung cancer have been recognized since Bayle (10), in 1810, reported his group of 3 cases. Pässler (115), in 1896, stated, "Actually from this abundance of material only a fraction can be used for our information on primary carcinoma of the lungs. First, because no cases without a post-mortem report can be considered and secondly, as has been emphasized already by some authors, those cases also have to be eliminated whose carcinomatous nature . . . cannot be considered as positive." Incredible as it may be, one may read in Sehart's work, published in 1904, that of 178 cases of lung cancer a correct clinical diagnosis was made in only 6 (75). This is some improvement, however, over the 100 per cent wrong diagnoses observed by Jeuther *et al.* (70) between 1894 and 1899. Sweany (153), after reviewing the problem of clinical diagnosis of lung cancer, concluded that at the beginning of this century the percentage of correct diagnoses was 5 per cent. In 1912, Adler (2) had this to say, "Is it not somewhat humiliating to realize that the difficulties of diagnosis are still so great as to prevent the best and most experienced medical men, with all the advantages of a large hospital, from discovering almost one-fifth of all carcinomata that come before them? . . . The physician must be imbued with the conviction that malignant pulmonary disease occurs much more frequently than is commonly believed and that he may meet it any day in his practice among the young, as well as among the old."

Difficulties in the diagnoses of lung cancer have continued to be recognized. It was pointed out by Adler (2) that "even the diagnoses made on the autopsy table are not always reliable. . . . It may happen also that the most careful and searching autopsy will not furnish the true diagnosis until a thorough microscopical examination has been made." Weller (164), after reviewing a group of 89 cases, found that the correct clinical diagnosis had been made in only 10 and suggested "with the additional aids now available the proportion of diagnosed cases should be very much

increased." Wells (166) found a diagnostic error of 36.5 per cent in a group of 578 cases of cancer studied in 1923, and he said, "Such a high ratio of incorrect diagnoses in a great hospital might seem to be evidence of something wrong with the hospital, but we find that other institutions dealing with a similar class of cases, in which most of the cancers coming to necropsy are of the internal organs, exhibit not dissimilar figures."

The clinical diagnosis of pulmonary cancer began to improve about 1915, although Scott and Forman (140), in 1916, found one correctly diagnosed case in their series of 4. In 1921, Lubarsch (92) found a correct diagnosis had been made in 240 of 458 cases, or 52 per cent. Barron (8), in 1922, approached the problem of the diagnosis of lung cancer in a different manner from that of others; he said, "Undiagnosability simply resolves itself into unfamiliarity with the more or less characteristic signs and symptoms." Considerable attention was given in 1927 by Probst (124), Wahl (160), and Katz (73) to this problem of the diagnosis of lung cancer. Probst (124) found that the correct clinical diagnosis had been made in 36.9 per cent of the 65 cases he reviewed and he deplored this low percentage "in spite of systemically applied x-ray examination." He cited the observation that "according to Bilz, Lubarsch, Sachs, Seyfarth, and others the diagnosis is made correctly in about 50 per cent." Sweany (153) considered the correct percentage diagnosis "had barely risen to 47 per cent" in 1925. Fried (40), in 1925, found only 2 cases in a group of 10 that were correctly diagnosed antemortem at the Peter Bent Brigham Hospital in Boston. Physicians in 1926 and 1930 were being warned to include carcinoma of the lung in their differential diagnoses (38, 39). Although by 1926 there were the additional aids of x-rays and the bronchoscope for the diagnosis of lung cancer, Fishberg (38) pointed out that a careful history and physical examination were of much greater importance than x-rays, particularly in the recognition of early cases.

It would seem to me that by 1930 there had occurred a marked improvement in the clinical diagnosis of pulmonary cancer. We would estimate this to be about 50 per cent in the practice of the better physicians, clinics, and hospitals. Obviously the percentage of correct diagnosis would be progressively lower in the practice of

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those who had less training and who did not have access to adequate diagnostic facilities. This fact becomes a most important one when attempting to establish the frequency of lung cancer between 1900 and 1930. Adler (2), commenting on this problem in 1912, said, "The death certificates on which burial permits are officially given are often ludicrously insufficient. For this reason the United States Census is entirely useless for our purposes . . . . It is therefore impossible to say, from the figures given by the United States Census concerning causes of death, how many persons mentioned as having died from tuberculosis, pneumonia or kindred diseases, may not really have died from lung tumors." This skepticism in America regarding the value of vital statistics for establishing the frequency of tumors likewise was expressed by Weller (163), Professor of Pathology at the University of Michigan, and by Wells (166), Professor of Pathology at the University of Chicago.

Hoffman (58), in 1929, pointed out that the Census Office in 1914 made the first attempt to present a comprehensive statement on cancer. In that year the death rate for cancer of the lung was 0.6 per 100,000 of the population and in 1924 it had increased to 1.6. Obviously this was a tremendous increase in a period of only 10 years. A most conspicuous feature of the statistics, as reported by Hoffman, was the variation in the frequency of cancer of the lung in the United States and in Canada. Between 1919 and 1923 the rate for Albany, New York was 2.5 and for the white population of New Orleans it was 2.8. From 1920 to 1924 the rate for San Francisco was 4.7, Boston 3.9, Province of British Columbia 2.1, Province of Saskatchewan 0.5, and for the city of Winnipeg 3.3.

Gilliam (45), Chief of the Epidemiology Section of the National Cancer Institute, recently pointed out that "the International Lists of Causes of Death did not separately list cancer of the lung and pleura, or even cancer of the respiratory system as a whole, until the Fourth Revision—first used in 1930. . . . Prior to 1930 the term bronchogenic carcinoma was lumped with 90 other cancers of various sites. Between 1930 and 1938, when this diagnosis appeared on a death certificate, it was tabulated with cancer and other malignant tumors of other respiratory organs (47C), that is, with tumors other than those designated as larynx (47A) or as lungs and pleura (47B). It was not until the Fifth Revision

came into use in 1939 that deaths which physicians charged to bronchogenic carcinoma were separately identified in official statistics."

All the literature supports the opinion that cancer of the lung has progressively increased since 1810. Gilliam (45) stated that "the rate of increase in recorded mortality was greatest in this country (America) between 1914 and 1930 and that it has been declining since." It was so common in 1927 that Weller (163) referred to it figuratively as an "epidemic." During the period from 1900 to 1930 a tremendous number of statistical studies based upon autopsies was made in France (62, 89, 106), Germany (15, 21, 22, 72, 73, 76, 92, 125, 160, 169), Russia (86, 112, 117, 121), England (19, 30, 33, 65, 104, 114, 145), Holland (31), Austria (36, 97), Italy (29, 158), Brazil (96), Switzerland (124), Czechoslovakia (99), Spain (28), Canada (20, 57, 80), Hungary (172), Denmark (64), Argentina (152), and America (8, 18, 40, 46, 47, 50, 90, 94, 131, 163, 165).

Excellent reviews on the increase of pulmonary cancer were included in the papers by Wahl (160), Probst (124), Katz (73), Weller (163), Barron (8), Moise (107), and Brunn (26). Probst (124) compiled data from 24 statistical studies made in Europe. After the elimination of those with incomplete figures, there were 88,750 autopsies which were performed between 1900 and 1925; in this particular group of autopsies 4.3 per cent of all cancers were pulmonary. In 30,468 autopsies performed between 1892 and 1931 by Americans, 5.5 per cent of all cancers were primary in the lung (40, 43, 71, 81, 94, 100, 107, 131, 149, 150, 163).

Between 1900 and 1930 there was one point that many investigators often wished to establish, and that was, "Is the increase in cancer of the lung real or only apparent?" Adler (2), in 1912, expressed the opinion that "there seems hardly room for doubt that the increase in the percentage of lung tumors is to be attributed mainly to the increased attention paid to these types of tumors and the greater care and more extensive microscopic investigation with which autopsies are carried out at present." Barron (8), in 1922, concluded that "not only is there an absolute increase in the number of cases but there is a three fold relative increase." Probst (124), in 1927, thought that the increase might be only apparent and due to more accurate and finer diagnosis. Huguenin (62), in 1928, said,

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"We cannot form an opinion on the relative frequency; we can only affirm that primary cancer in the lung is not rare." Schall (135), in 1928, felt that it remained an open question whether there had been a true or an apparent increase due to more accurate diagnosis. Homann (59), in 1930, reviewed the available literature, discussed the alleged increase in frequency of lung cancer during recent years, and concluded that the increase was apparent and not real. This increase, according to Homann, may be influenced by the bronchoscopic, roentgenographic and histologic techniques. Von Glahn (46), in 1930, said the available statistics left him "in doubt as to whether there has been an actual increase of lung cancer."

Cancer of the lung in 1905 occupied fifth place among malignant tumors and in 1925 it had reached second place (156). In the region of Trieste, Italy, Ferrari (37) observed that before 1910 cancer of the lung occupied eighth place, fourth place between 1911 and 1920, and by 1921 to 1926 it was in second place. Barron (8), in 1922, considered carcinoma of the lung sixth among all malignant conditions, while in 1930, according to Rosahn (131), it was in fifth place. Cancers of the lung and bronchi were found to be second in frequency to cancer of the stomach in a group of 22,139 cases collected between 1925 and 1933 (32). This progressive increase in cancer of the lung is interesting in view of what King and Newsholme (79) pointed out in 1893: "The increase in cancer is only apparent and not real, and is due to improvement in diagnosis and more careful certification of the causes of death. This is shown by the fact that the whole of the increase has taken place in inaccessible cancer difficult of diagnosis, while accessible cancer easily diagnosed has remained practically stationary."

In 1930 we find unanimity in the increase of cancer of the lung; however, a division did exist as to whether this increase was real or only apparent. Hamman (51), in discussing the confusion referable to the statistics on cancer of the lung, said that there were not sufficient data to settle the dispute whether the increase was real or apparent, and noted that "two authors, Rosahn and Fried, using the same statistical material, arrived at opposite conclusions." Rosahn wrote that the postmortem incidence of primary carcinoma of the lung was steadily increasing and this increase was real and absolute,

while Fried stated that the increase was very likely more apparent than real.

It has been pointed out in many of the statistics that cancer of the lung occurred more frequently in men from 50 to 70 years of age (62, 63, 76, 115, 124, 160). Karrenstein (72), in 1908, found the average age of patients with cancer of the lung to be 55.4 years. Weller (164), in 1913, observed that most of his cases occurred between the ages of 56 and 60 years. Brunn (26), in 1926, found 90 per cent of his cases occurring between the ages of 40 and 80. Hanf (54), in 1927, observed the greatest frequency between the ages of 50 and 54 years. Simons (144), in 1937, compiled 2,796 cases of cancer of the lung and found that 80 per cent occurred between the ages of 40 and 70 years. In 1926, Thomas (155) noted that "for centuries before and after the time of King Tut, down to the discovery of America, the average length of life was 18 years; at the time of the French Revolution it had increased to 33 years; at the time of our own Civil War it had advanced approximately to 45 years; at present it is about 57 years, and the longed for 70 may be reached within the next 50 years, maintaining the present ratio of medical progress. Ten of these added years have been contributed to in the last two decades." The importance of such facts, according to Fried (41), is evident in connection with the well known cancer age. Fried also said that the increase in cancer of the lung may be due to progress in hygiene and preventive medicine resulting in increased human longevity.

A higher frequency of cancer of the lung in the male than in the female was first recognized during the latter half of the nineteenth century (115). This variation has persisted until the present. However, Kaufmann (74) reported that in Basle cancer of the lung was more frequent in the female than in the male. This difference in frequency between the male and female has served as one of the major factors in the attempt to establish an etiology for this particular neoplasm and to account for its progressive increase. Pässler (115), in 1896, in a group of 68 pulmonary neoplasms, found 50 males and 18 females. In the 374 cases collected by Adler (2) in 1912 the percentage of males was 71.9. In Weller's (164) group in 1913 there were 70 males and 17 females. Biberfeld (15) collected 600 cases from the literature and found the ratio to be 3 to 1. Breckwoldt (21), in 1926, in a group of 1,087 cases found the ratio to be 2.88 to 1. In 1931, Verga and Botteri

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(158) compiled 9,845 cases of lung cancer and found an incidence of 76.2 per cent for the males. Simons (144), in 1937, tabulated 5,121 histologically proved cases and found a ratio of 4 to 1 in favor of the male. Thus, we find the ratio of pulmonary cancer in the male and female to be 3 or 4 to 1 during the period from 1900 to 1930.

The increase in cancer of the lung that began in the nineteenth century had reached such proportions by 1910 to 1915 that every effort was being put forth to explain it on an etiologic basis. An association between pulmonary cancer and tuberculosis had been observed frequently before 1900 as well as after this date. The theory of an incompatibility between tuberculosis and pulmonary cancer, as advanced by Rokitsansky (130) in 1855, apparently was not correct. Friedländer (42), as early as 1885, had observed lung cancer in the wall of tuberculous cavities. Similar observations were made by Schwalbe (138) and Perrone (118). Barron (8), in 1922, in discussing the etiology of lung cancer said, "Perhaps the chief etiologic factors are inflammatory conditions, and of these, tuberculosis is the most important." Cherry (27), in 1925, expressed the opinion that "cancer is in most cases the expression of the resistance of the cells to a second or subsequent invasion by the bacillus tuberculosis." Ewing (34), as late as 1928, considered tuberculosis as the cause of pulmonary cancer. Syphilis, like tuberculosis, was also considered to be the etiology of lung cancer; however, the association was less impressive than that of tuberculosis (98, 122).

The early observations on tuberculosis and syphilis prepared the way for the theory of chronic irritation as the etiology of lung cancer, a theory that gained considerable support after 1910 and continued to be the prevailing one long after 1930. Adler (2), in 1912, said, "Chronic irritations affecting the respiratory organs are numerous and are supposed by many to play a very active part in the causation of tumors of the lung." If irritation is accepted as an important etiologic factor, carcinoma of the lung would be in line with many other forms of cancer (145).

Closely associated with the hypothesis of chronic irritation was that of metaplasia. Wahl (160), in 1927, emphasized this relation when he said, "We see therefore that in epithelial metaplasias the chronic irritations play a deciding part." Pässler (115), in 1896, pointed out the possibility of a relationship between meta-

plasia and cancer of the lung. Watsuji (162), in 1904, observed that 32.3 per cent of all pulmonary carcinomas that he investigated was "built up" from pavement epithelial cells. Subsequent investigators have pointed out the frequency of squamous cell carcinomas originating from the columnar epithelium lining the pulmonary bronchi. As late as 1927, Katz (73) had this to say referable to metaplasia and cancer, "The link in which the fact of chronic inflammation is connected with the observation of the subsequent cancer, which at first was of a purely temporal nature but is now recognized as causal, is closed: the metaplasia . . . . There is no doubt that the process of metaplasia creates a ground for the cancerization. And it is likewise undeniable that this metaplastic process is the result of a chronic state of irritation. Yes, one can say: that metaplasia is a precancerous state, without saying that now a carcinoma must always develop from each metaplasia."

Influenza received considerable attention after 1918 as a specific agent in the etiology of lung cancer. Askanazy (4), in 1919, apparently was the first to point out that metaplasia may occur in the lungs in influenza. He warned, however, against overestimating its role in the etiology of lung cancer for "individual cases of lung cancer one cannot know whether the metaplasia is a cause or a consequence of tumor formations." Askanazy's observation of metaplasia in the lungs after influenza was confirmed by Schmidt-mann (136) and Teutschlaender (154). Bauer (9), in 1921, was one of the first to report a case of pulmonary carcinoma, giving "grip" as a significant factor in the history. Meyer (105), in 1922, also reported a case of lung cancer following "grip." Moise (107), in 1921, Barron (8), in 1922, and Berblinger (12), in 1925, thought influenza was a primary factor in the increase of lung cancer. Winternitz *et al.* (170), in 1920, Wahl (160), in 1927, Katz (73), in 1927, and Huguenin (62), in 1928, concurred in this opinion. Simpson (145), in 1928, in discussing this problem of influenza and lung cancer had this to say, "The fact that the increase continued for several years after the influenza epidemic cannot be considered to rule out its aetiological importance, as it is known that irritative factors may not produce results until some time after they have ceased to operate."

Apparently there were as many investigators who rejected the theory of the relation of influ-

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enza to cancer of the lung as accepted it. Gottstein (48), in 1923, found no relation between "grip" and lung cancer. This opinion was concurred in by Staehelin (148) in 1925 and Hueper (61) in 1926. Seyfarth (141), Kikuth (76), and Hoffman (58) found only a few histories of influenza in their cases of lung cancer. Krompecher (84) maintained that no increase in lung cancer resulted from influenza in the Budapest material collected up to 1924. Probst (124), Wahl (160), and Mönckeberg (109) discussed this problem of the relation of influenza to lung cancer. The former pointed out that since lung cancer had been increasing almost continuously since 1910 in Zurich he could not support the idea that the increase was due to influenza. Hueper (61) did not find an increase in the incidence of pulmonary cancer after the epidemic of 1889-1894. Niskanen (111) wrote in 1949 that cancer of the lung was rare in Iceland although the epidemic was most severe. As late as 1948, Fried (40) said, "The conception that the alleged increase in bronchiogenic cancer is a sequel to influenza cannot be relied upon."

Interest in the etiology of lung cancer between 1900 and 1930 continued to center around infectious processes that produced chronic irritation with an associated metaplasia. McKenzie (101) and Haythorn (55) had observed metaplasia after pneumonia in 1907 and 1912. Siegmund (143), in 1922, reported 3 cases of pulmonary cancer in which there was bronchiectasis which he thought resulted from measles, whooping cough, grip, pneumonia, and chronic bronchitis.

The study of the pulmonary lesions in the Schneeberg mines during the latter part of the nineteenth century emphasized the importance of pulmonary irritation produced by non-bacterial agents as a possible etiology of pulmonary cancer. Pulmonary irritants associated with specific and nonspecific types of dust, chemicals, and irradiation, as observed in the Schneeberg mines, also were studied between 1900 and 1930 in an attempt to establish their relation to the increase in pulmonary cancer. Rostoski, Saupe, and Schmorl (133), in 1926, stated that 70 per cent of the miners that developed pneumoconiosis subsequently developed lung cancer. Staehelin (148) pointed out that miners elsewhere in the world showed no increase in the incidence of pneumoconiosis and pulmonary cancer. Rostoski (132), in 1924, noted that

pneumoconiosis leads more frequently to tuberculosis than to lung cancer. Uhlig (157), in 1921, thought that the inhalation of cobalt was really the cause of the lung cancer in the Schneeberg miners, but Heilmann (56), in 1925, thought it was due to the inhalation of stone dust. Berblinger (12) questioned whether nickel, cobalt, or arsenic was the real cause of these pulmonary cancers. Analyses of the lungs of the miners revealed calcium, magnesium, alum, silicic acid, chlorides, phosphates, but not a trace of arsenic, cobalt, bismuth, nickel, or uranium (13, 157). Risel (129) suggested that a gaseous arsenic combination resulting from fungi and oidia might be the cause of these pulmonary neoplasms. Schulte (137), after reviewing 487 cases of pneumoconiosis without finding one pulmonary carcinoma, suggested that in the Schneeberg mines the pulmonary cancers probably resulted from arsenicals coupled with the inhalation of large amounts of radium emanations. Others considered only radium emanations to be the cause of these neoplasms (123). Ludewig and Lorensen (93) found radium emanations up to 50 Mache units per liter of air in one of the Schneeberg mines and Santholzer (134) found up to 52 Mache units per liter of air in one of the Jachymov mines. Katz (73), in 1927 and after reviewing this problem, concluded that the etiology of the pulmonary lesions in the Schneeberg mines is an "unsolved problem."

Many other pulmonary irritants were carefully evaluated between 1920 and 1930 as possible etiologic agents for lung cancer. Hampeln (53), in 1923, proposed that lung cancer is a dust disease. Materna (99) in 1924, agreed with this opinion. Heilmann (56) showed that the pathologic changes in the lung produced by dust ultimately produced lung cancer. Berblinger (12), however, did not consider dust of itself a cause of lung cancer. Seyfarth (141) denied that any one kind of dust—street dust, metal dust, glass dust, or coal dust—could be held solely responsible for the increase in lung cancer. Probst (124) failed to find cancer of the lung more frequent in individuals such as road workers, drivers, policemen, chauffeurs, whose occupation exposed them to street dust. The observation that pulmonary cancer occurred in outdoor workers (33, 145) more frequently than in professional groups (23) emphasized an environmental factor to which males were exposed as the etiologic agent for cancer of the lung.

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According to Probst (124), Block in a lecture before the Association of Swiss Road Experts in 1924 discussed street tarring and suggested that it might be significant in the etiology of carcinomas in general. Stachelin (148), however, in 1925 could find no connection between the increase in the tarring of roads and the increase in carcinoma. Probst, in 1927, expressed a similar opinion. Vincent (159) thought that he could see a parallelism between the increase of cancer in general and the tarring of roads. Probst, in 1927, considered it questionable that street tarring alone had any causal relation to pulmonary carcinoma. Simpson (145), in 1928, expressed the opinion that "when one considers the widespread practice of tarring, the known potentialities of tar as an irritant factor, and the undue proportion of males in outdoor workers, it is obvious that here lies an urgent problem that demands scientific solution." Simpson regarded the rarity of lung cancer in Hong Kong and Singapore as due to the absence of tarred roads. Heilmann (56) thought that the increase in the frequency of lung cancer could be attributed to the effects of tar. Konrad and Franke (82) denied that the increase of the disease in Riga was due to either an increase in automobile traffic or the use of tar.

In 1925, the automobile was brought into this problem of lung cancer, not only from the fact that it ran across tarred roads but also because of its exhaust gases (56). Klotz (80), in 1927, called attention to the fact that "the cancer incidence of the lungs shows a parallelism with the increased use of gasoline engines, but we have no data that these two are in any way related." Probst (124) pointed out that coal tar fractions below 230 degrees under 1 to 2 mm. of Hg pressure contain little or no carcinogenic substance and that "the most active fractions were the ones between 250 and 293 degrees under 1 to 2 mm. of H pressure." The exhaust products of carburetor motors consist chiefly of carbon dioxide, nitrogen, water vapor, and varying amounts of carbon monoxide, hydrogen, and methane. Tars that are obtained from petroleum-like products exhibit an aromatic nature only when the decomposition temperatures are very high (900 degrees and above). It would appear that exhaust gases do not contain any compounds that are related to the tar constituents with which cancer has been produced in experimental animals (124).

Experimental observations were begun in 1923 and were continued for many years thereafter in an attempt to establish whether tars would produce cancer, especially pulmonary cancers. Kimura (78), in 1923, claimed to have produced cancer of the lung in a guinea pig following the intrabronchial insufflation of coal tar. Bonne (17), in 1927, injected coal tar intratracheally into 104 mice but did not observe any increase in lung cancer. Murphy and Sturm (110), in 1925, painted the skin of mice with coal tar and got an increase in pulmonary tumors. Möller (108) and Smith (146) exposed mice to coal tar fumes, automobile exhaust, and gasoline vapors, but found no increase in the frequency of lung cancer.

Specific chemicals have been suggested as the cause of lung cancer. Among these may be mentioned war gas (1). However, Hoffman (58), in 1929, said there was no evidence that exposure to irritant gases, including war gas, had been productive of lung cancer. Kikuth (76) reported a case of a pulmonary cancer in a chemist and suggested that chlorinated hydrocarbons could be held responsible. Certainly these isolated cases of lung cancer attributed to specific chemicals would not be a significant factor in the over-all increase of pulmonary cancer. Since this fact was realized many years ago, other etiologic agents were diligently sought for; among these were smoke and chemical impurities in the atmosphere (53, 56). Duguid (33), in 1927, felt that it "must be some specific constituent of the pollution rather than the general atmospheric pollution itself that should be suspected, because the atmospheric conditions in cities are generally supposed to be improved since the coming into operation of the Smoke Abatement Acts (England), and were it simply a matter of a smoke-laden atmosphere, the incidence of thoracic tumors would be expected correspondingly to be on the decrease."

As early as the end of the nineteenth century Soemmering (147) suspected smoking to be associated with pulmonary cancer. At the turn of the century Brosch (24), apparently the first, succeeded in producing malignant proliferation in the skin of guinea pigs by smearing the skin with "tobacco juice." Geipel (44), in 1899, Seyfarth (141), in 1924, and Kikuth (76), in 1925, noted cases of lung cancer in cigar makers. In 1912, Adler (2) had this to say about tobacco as a factor in the etiology of lung cancer, "The do-

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mestic life led by women, with their consequent retirement and immunity from the irritations and traumatisms which must be frequent in the more unprotected life of men (the abuse of tobacco and alcohol, the many trades and vocations which are accompanied by irritations of the respiratory organs, etc.) has been adduced in explanation of this fact." Fahr (35), in 1923, and Seyfarth (141), in 1924, associated cigarette smoking with cancer of the lung. Fahr thought the inhalation of cigarette smoke, which was becoming more frequent, would explain the increased frequency of lung cancer in the male. Staehelin (148), in 1925, expressed the opinion that "the mere fact that there are more men than women smokers and more male than female cases of lung cancer is not sufficient proof of the etiologic influence of smoking." Kikuth (76), in 1925, found a history of smoking infrequently in his cases and expressed the opinion that "pulmonary carcinoma would have to occur much more frequently among those who smoke to excess before this could be regarded as a big factor." Katz (73), in 1927, noted that cancer of the lung was not particularly frequent in the Orient where there was heavy smoking. Huguenin (62), in 1928, in discussing the relation of smoking to cancer said, "Beside the fact that this argument could cause a smile today, no fact of investigation any longer supports the role of smoking or tobacco intoxication." Hoffman (58), in 1929, stated, "There is no definite evidence that smoking habits are a direct contributory cause toward malignant growths in the lung." McNally (103), in 1932, pointed out that the increase in lung cancer parallels the increase in the consumption of cigarettes and, because of this, one is certainly led to believe that cigarette smoking is an important factor in the increase in frequency of the disease. However, in 1934, Sweany said, "If there is any merit in this theory, it should be manifest in the female sex, where the increase in the use of cigarettes has been greater than in men. If, for example, the ratio of men to women 20 years ago was 3 to 1, and now in 1932 it is 1.5 to 1, the case is well nigh proved. So far, no such increase in ratios has appeared, for the sex ratio was and still is around 3 males to 1 female, similar to other malignant conditions other than those of sex differences. On the other hand, there are many patients with lung cancer who do not give a history of cigarette smoking at all" (153).

Few, if any, investigators today consider

trauma a factor in the etiology of lung cancer; however, as late as 1930 Wells and Cannon (167) reported a case of pulmonary cancer in which trauma was considered to be the etiology. In 1913, Weller (164) collected 89 cases of lung cancer from the literature, in 3 of which the disease was attributed to trauma; he said, "We may, therefore, be certain that gross trauma is not an important etiologic factor." As for all of the proposed etiologic agents for cancer of the lung, there were some who supported trauma, at least they reported cases in which trauma had occurred (6, 38, 76, 119, 141, 148), and others who objected to the theory of trauma and lung cancer (8, 34).

Heredity as a factor in the etiology of pulmonary cancer had its supporters and nonsupporters in the interval between 1900 and 1930. Adler (2), in 1912, expressed the opinion that the incidence of malignant growths of the lung did not appear to be seriously affected by heredity. Huguenin (62), in 1927, said, "Whatever opinion one professes with regard to the primary cause of cancer, its pulmonary localization does not seem to be the result of chance; hereditary changes or acquired ones govern the development of malignant tumors of the lung; such at least are the reflections which the discoveries of our predecessors suggest." Weller (163), in 1929, voiced the conviction that heredity might be a significant etiologic factor in the production of these neoplasms. He suggested "the development of carcinoma of the lungs may be found to be due to an inheritable intrinsic predisposition which may be activated by a variety of chronic irritative factors." Schwyter (139) found congenital malformations of the lung in the neighborhood of the growth in 6 cases and as a result concluded that heredity or developmental errors might be the cause of pulmonary cancer.

Although primary attention had been given to the etiology and frequency of lung cancer during the period 1900 to 1930, there also was an increasing number of papers discussing diagnosis and treatment. There was a diagnostic procedure being investigated before 1900 (128) that ultimately proved to be a most valuable one in lung cancer. This was the demonstration of microscopic particles in the sputum of individuals with pulmonary cancer. The early investigators usually used fresh unstained sputum; however, in 1910, Ballet (7) stained the smears with picro-

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carmine. In 1913, Bezancon and de Jong (14) fixed the smears in a 1 per cent solution of chromic acid and then stained them with a polychrome stain. Sternberg (151), in 1923, and Homann (60), in 1929, suggested the technique of embedding the cells in paraffin and cutting sections. It was pointed out, however, that serial sections were necessary with the latter technique. Some investigators contended that sputum examination was not practical because of cell autolysis (83). Typical neoplastic cells were found in the sputum of 13 of 25 cases by Hampeln in 1918 (52). Brunn (26), in 1926, expressed the opinion that sputum should be examined thoroughly as several cases of carcinoma of the lung had been diagnosed by the finding of tumor shreds and cells.

The roentgen rays, first described in 1895, soon were used in the diagnosis of lung cancer. Leo (88), in 1898, diagnosed a metastatic osteosarcoma in the lung with roentgen rays. Immelmann (66), in 1899, pointed out that "the x-ray diagnosis of diseases of the lungs and of the pleura, among which principally pneumonia, gangrene, tumors, tuberculosis and pleuritis are capable of throwing shadows on the screen, is a diagnosis 'per exclusionem' in the true sense of the word." Walsham and Beale (161), in 1900, in discussing skiagraphy in the diagnosis of chest diseases did not mention roentgen rays for the diagnosis of lung cancer. After discussing the roentgenographic findings, in 1906, in lung abscesses, gangrene, pneumonia, emphysema, collapse of the lung, effusion, pneumothorax, and hydrothorax, Pfahler (120), Director of the Roentgen Ray Laboratory at the Medico-Chirurgical Hospital in Philadelphia, said, "The greatest field of usefulness of the roentgen rays in lung diseases is the study of tuberculosis." Otten (113), in 1906, was the first to report the use of roentgen rays in the diagnosis of primary lung cancer and his article is accompanied by illustrations of the roentgenograms.

Adler (2), in 1912, had this to say about roentgen rays, "It was not very long ago that Frankel wrote that the x-rays were of little service in the diagnosis of lung tumors. Since then the x-rays have become a most remarkable and efficient aid to diagnosis in general, and there exists the well-founded hope of their increasing efficiency as further improvements in the apparatus and advances in technique are made." McMahon and Carman (102), in 1918, ex-

pressed the opinion that "in most instances the roentgen findings in primary carcinoma of the lungs are pathognomonic of the disease, and may be the first to suggest the exact nature of the pulmonary lesions." Four years later Barron (8) stated that many authors found the roentgenograms either of negative value or at times misleading. Maclachlan (95), in 1923, likewise questioned the value of x-rays in the diagnosis of pulmonary neoplasms. Huguenin (62), in 1927, pointed out that one might say that repeated radioscopic examination could be a factor in tumor proliferation in the lung. Although the discovery and increased use of the roentgen rays coincided with the increase in lung cancer, there is no proof that x-rays are a cause of cancer, but the possibility should be recognized (144).

Although therapeutic use of the roentgen rays had been suggested, Barron (8), in 1922, expressed the opinion that thus far it was of little or no value in treatment. Davidson (30), in 1930, thought that the x-rays possessed a very definite value in treatment, but should be classed among the palliative remedies as the benefits therefrom were only temporary. Kerley (75), in 1928, could find "no reports dealing with radium therapy, although this would appear to be the only rational method of treating the disease when it is seen late or when its origin is in an upper lobe bronchus close to vital structures. With our present knowledge of radium, it is probable that heavy external radiation of the chest, properly administered, would at least ameliorate the distressing dyspnea which is so constant a feature of lung cancer." Goltz (47), in 1930, said, "The treatment for this condition demands early diagnosis and since carcinoma of the lungs is usually carcinoma of the larger bronchi, local cautery and possibly radium by a skillful bronchoscopist offers the best hope." Among general remedies for lung cancer, selenium and copper were used according to Atkinson (5); however, he pointed out that the intravenous use of lead appeared to be a promising method of treatment.

The technique of direct bronchoscopy, first described in 1898 by Killian (77), soon was recognized as a valuable aid in the diagnosis of lung cancer. Renon and his associates (127), in 1910, recommended the use of the bronchoscope and the taking of biopsies from bronchial tumors. Adler (2), in 1912, had this to say about the bronchoscope, "It cannot be denied that the

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field of bronchoscopy may be greatly extended by improvements in apparatus and in technique. It is, however, the writer's opinion that its usefulness in the diagnostics of lung tumors, at this present writing at least, is limited." Chevalier Jackson (68), in 1917, removed an endothelioma from the right bronchus with the bronchoscope. Barron (8), in 1922, while speaking of bronchoscopy and pulmonary biopsy said, "Both are so difficult to perform that their use is not to be encouraged at the present time." MacLachlan (95) only a year later expressed the opinion that bronchoscopy had proved to be one of the most valuable diagnostic aids as yet offered. Others expressed a similar opinion (91) (67).

Sicard and Forestier (142), in 1922, introduced lipiodol as an aid in the diagnosis of pulmonary lesions. Its advantages and disadvantages were discussed in articles by Brown (25) and Archibald and Brown (3).

Benda (11), in 1904, commented on the fact that cancer of the lung occupied a unique position, inasmuch as it was the only cancer that was absolutely beyond the reach of the surgeon. He went a step further and added that, no matter what progress surgery might make, it could never hope to deal satisfactorily with lung cancer, as it would always remain impossible to make the diagnosis early enough for any reasonable expectation of a cure by surgical interference. About 1912 Jacobaeus (69) was one of the first to employ thoracoscopy in the diagnosis of lung cancer. However, in 1930, Davidson (30) said that surgery had reached a stage in which the exploration of the chest presented difficulties no greater than those of opening the peritoneal cavity, but that thoracoscopy still had its advantages. The first pneumonectomy for cancer of the lung apparently was performed in 1910 by Kümmell (85); the patient died on the sixth postoperative day from a septic infection of the operative site. Lenhartz (87), in 1910, reported the removal of a lobe for pulmonary cancer. The first successful total pneumonectomy for pulmonary cancer was performed in 1933 by Graham and Singer (49).

In attempting to summarize the progress in our knowledge of cancer of the lung during the period from 1900 to 1930, it would seem that one of the most important contributions was the demonstration that this neoplasm was more frequent than it was formerly thought to be. Opinions, however, were divided as to whether

this increase was real or only apparent. Many agents were investigated as possible causes for the increase in frequency of lung cancer; some were proved to be unlikely, while others, such as cigarette smoking and air pollution, were carefully studied after 1930.

Significant advancements were made between 1900 and 1930 in the diagnosis and the treatment of pulmonary cancer. The use of x-rays was more or less perfected as a diagnostic procedure. Surgery was developed to such a point that the first successful pneumonectomy for lung cancer was performed in 1933. The clinical diagnosis of this lesion greatly improved after 1900. By 1930 the correct diagnosis of lung cancer was being made in approximately 50 per cent of the cases by the better physicians who had access to the latest diagnostic facilities, such as x-rays and cytological examination of sputum.

Scientific interest in cancer of the lung continued to progress after 1930 with emphasis on its frequency, etiology, and treatment. Few diseases have had a more exciting history than that of lung cancer.

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